PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference GRFBP6230874	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2004/002512	International filing date *(day/month/year)* 14.06.2004	Priority date *(day/month/year)* 13.06.2003
International Patent Classification (IPC) or national classification and IPC A61K39/21, A61K39/285, A61K38/00, A61P31/12		
Applicant PALMOWSKI, Michael J. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.04.2005	05.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Renggli, J Telephone No. +49 89 2399-7461

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002512

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-31	as originally filed
Claims, Numbers	
1-37	received on 15.04.2005 with letter of 12.04.2005
Drawings, Sheets	
1/7-7/7	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-18,31-37

because:

☒ the said international application, or the said claims Nos. 1-18,31-37 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002512

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	10,28,35
	No:	Claims	1-9,11-27,29-34,36,37
Industrial applicability (IA)	Yes:	Claims	19-30
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 31-37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: Tellier et al., AIDS, 1998, Vol. 12, pp. 11-18
D2: WO 98/21354
D3: Yang et al., J. Virology., Jan. 2003, Vol. 77(1), pp. 799-803
D4: Esslinger et al., J. Clin. Invest., 01.06.2003, Vol. 111(11), pp. 1673-1681

2. Document D1 discloses the use of a heterologous prime-boost strategy for treating FIV. Specifically, (I) a recombinant canarypox virus expressing FIV immunogens has been used in combination with (ii) FIV-infected lymphoid cells for protecting cats against FIV. This immunization schedule enabled the protection of cats against homologous an heterologous challenge (see page 12-page 13, bridging paragraph; page 16, right-hand column, last complete sentence; page 17, right-hand column, sentence "In our study...-end of document").

D1 does not apparently disclose the use of an engineered lentivirus vector or of an APC transduced with said vector. Thus claims 1-37 can be considered to be novel over D1.

Document D2 discloses an heterologous prime-boost immunisation characterized by the injection of canarypox ALVAC expressing env, gag/pro of FIV (Days 0 and 28) and the injection of inactivated FIV cell vaccine (day 56). This protocol enabled the protection of cats against homologous or heterologous challenge. This document also discloses protocol in which the priming composition may be used as boosting composition (see pages 77-92; claims 25-28).
D2 does not apparently disclose the use of an engineered lentivirus vector or of an APC transduced with said vector. Thus claims 1-37 can be considered to be novel over D2.

3. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9, 11-27, 29-34, 36 and 37 does not involve an inventive step in the sense of Article 33(3) PCT.

It has been indicated that it is difficult for the skilled person to predict whether an heterologous prime-boost regimen will work or not. This fact is known in the field, (see document D4, page 1680, left-hand column, 3rd full paragraph).

In view of this statement, it thus appears that an inventive step can only be acknowledged for the specific combinations and successful combinations disclosed in the present application.

In the experimental part of the application, one scheme tested is: priming=DC transfected with lentivirus, and boosting=vaccinia.

The other scheme tested is: priming=naked DNA, boosting=lentivirus particles.

Both protocols led to a high CTL response.

In view of these facts, it thus appears that an inventive step can only be acknowledged for the claims limited to these successful combinations.

This fact seems not to be contested by the applicants who indicated that it is not possible to predict that a product useful as a priming composition would be useful when used as a boosting composition.

Thus an inventive step could only be acknowledged for the specific combinations indicated above.

Presently, only claims 10, 28 and 35 would appear to contain this limitation.

The problem to be solved by claims 10, 28 and 35 can be defined as the provision of an alternative prime-boost regimen in view of document D3.

The solution lies in the use of a nucleic acid (priming) and a lentiviral vector (boosting).

An inventive step can be acknowledged for said claims in view of the unpredictability associated with the immunization protocols.

In the absence of evidence, no inventive step can on the contrary be acknowledged for claims 1-9, 11-27, 29-34 and 36, 37 of the present application.

Additional remarks:

Claims 31-37 are considered to be unclear, since the wording "for the priming or boosting of an immune response against the antigen in a heterologous prime-boost immunisation" does not define a disease or the medical use of the product (Art. 6 PCT).

Re Item VI
Certain documents cited

The present opinion is given assuming that the claimed priority is valid. The document Palmowski et al., J. Immunol., Feb. 2004, pp. 1582-1587, Vol. 172 is therefore not relevant for the examination of novelty and inventive step at present. However, the attention of the applicant is drawn to the fact that this document may be relevant in the examination of novelty and inventive step for those parts of the application, if any, which do not have a

valid claim to priority.

Claims:

1. A method of stimulating an immune response to an antigen in an individual by a heterologous prime-boost immunisation protocol, the method comprising the steps of:

i) administering to the individual a priming composition encoding or containing said antigen to prime said immune response;

ii) administering to the individual a boosting composition encoding or containing said antigen to boost the primed immune response,

wherein one of said priming or boosting compositions comprises lentivirus engineered to comprise nucleic acid encoding said antigen, or an antigen presenting cell transduced in vitro with a lentiviral vector engineered to comprise nucleic acid encoding said antigen.

2. A method according to claim 1 wherein the other of said priming or boosting compositions comprises one or more of:

i) a nucleic acid encoding said antigen;

ii) one or a plurality of peptides, each peptide comprising an epitope, wherein one of said epitopes is said antigen;

iii) a viral vector comprising nucleic acid encoding said antigen;

iv) antigen presenting cells transduced in vitro to express said antigen;

v) a vector, preferably a viral vector, having nucleic acid encoding a plurality of peptides, each peptide comprising an epitope wherein one of said epitopes is said antigen.

3. A method according to claim 2 wherein the viral vector of iii) is a pox virus having a modified genome encoding said antigen.

4. A method according to claim 2 wherein the viral vector of (iii) is a lentiviral vector engineered to comprise nucleic

acid encoding said antigen and wherein the envelope of the lentivirus of one of the boosting or priming compositions is immunogenically different to the other.

5. A method according to claim 1 wherein the priming composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and the boosting composition comprises a pox virus having a modified genome encoding said antigen.

6. A method according to claim 3 wherein the pox virus is a vaccinia virus.

7. A method according to claim 2 wherein the nucleic acid of i) is a plasmid or other expression vector.

8. A method according to claim 2 wherein the antigen presenting cells of iv) are dendritic cells transduced in vitro by a lentivirus engineered to comprise nucleic acid encoding said antigen.

9. A method according to claim 1 wherein the priming composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and the boosting composition comprises an immunologically different lentiviral vector engineered to comprise nucleic acid encoding said antigen.

10. A method according to claim 1 wherein the priming composition comprises a nucleic acid encoding said antigen, and the boosting composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen.

11. A method according to claim 1 wherein the priming composition comprises a pox virus having a modified genome encoding said antigen, and the boosting composition comprises

a lentiviral vector engineered to comprise nucleic acid encoding said antigen.

12. A method according to claim 1 wherein the priming composition comprises antigen presenting cells transduced in vitro with a lentiviral vector engineered to comprise nucleic acid encoding said antigen, such that the cells express said antigen, and the boosting composition comprises a pox virus having a modified genome encoding said antigen.

13. A method of boosting a pre-existing immune response to an antigen in an individual, the method comprising the step of administering to the individual lentivirus particles engineered to comprise nucleic acid encoding said antigen, said individual having been previously exposed to said antigen but not having previously been exposed to said lentivirus particles.

14. A method according to claim 13 wherein the individual has previously been exposed to said antigen by administration of nucleic acid encoding the antigen.

15. A method according to claim 14 wherein the nucleic acid is a plasmid or other expression vector.

16. A method according to claim 13 wherein the individual has previously been exposed to the antigen by administration of a pox virus having a genome modified to encode the antigen.

17. A method according to claim 13 wherein the individual has previously been exposed to said antigen by administration of a lentivirus engineered to comprise nucleic acid encoding said antigen, wherein the envelopes of the two lentiviruses are immunologically different to one another.

18. A method according to claim 13 wherein the individual has previously been exposed to the antigen by infection with a pathogen or development of a cancer.

19. A kit for stimulation of an immune response against an antigen by a heterologous prime-boost immunisation protocol, the kit comprising (i) a first pharmaceutical composition, encoding or containing said antigen, to prime an immune response against said antigen; and
ii) a second pharmaceutical composition, encoding or containing said antigen, to boost the immune response against said antigen;
wherein at least one of said priming or boosting compositions comprises lentivirus engineered to comprise nucleic acid encoding said antigen, or an antigen presenting cell transduced in vitro with a lentiviral vector engineered to comprise nucleic acid encoding said antigen such that the cell expresses the antigen.

20. A kit according to claim 19 wherein the other of the priming or boosting compositions comprises one or more of:
i) a nucleic acid encoding said antigen;
ii) one or a plurality of peptides, each peptide comprising an epitope, wherein one of said epitopes is said antigen;
iii) a viral vector comprising nucleic acid encoding said antigen;
iv) antigen presenting cells, e.g. DC, transduced in vitro to express said antigen;
v) a vector, preferably a viral vector, having nucleic acid encoding a plurality of peptides, each peptide comprising an epitope wherein one of said epitopes is said antigen.

21. A kit according to claim 20 wherein the viral vector of iii) is a pox virus having a modified genome encoding said antigen.

22. A kit according to claim 20 wherein the viral vector of (iii) is a lentiviral vector engineered to comprise nucleic acid encoding said antigen and wherein the envelope of the lentivirus of one of the boosting or priming compositions is immunogenically different to the other.

23. A kit according to claim 20 wherein the priming composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and the boosting composition comprises a pox virus having a modified genome encoding said antigen

24. A kit according to claim 21 wherein the pox virus is a vaccinia virus.

25. A kit according to claim 20 wherein the nucleic acid of i) is a plasmid or other expression vector.

26. A kit according to claim 20 wherein the antigen presenting cells of iv) are dendritic cells transduced in vitro by a lentivirus engineered to comprise nucleic acid encoding said antigen.

27. A kit according to claim 20 wherein the priming composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and the boosting composition comprises an immunologically different lentiviral vector engineered to comprise nucleic acid encoding said antigen.

28. A kit according to claim 20 wherein the priming composition comprises a nucleic acid encoding said antigen, and the boosting composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen.

29. A kit according to claim 20 wherein the priming composition comprises a pox virus having a modified genome encoding said antigen, and the boosting composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen.

30. A kit according to claim 20 wherein the priming composition comprises antigen presenting cells transduced in vitro with a lentiviral vector engineered to comprise nucleic acid encoding said antigen, such that the cells express said antigen, and the boosting composition comprises a pox virus having a modified genome encoding said antigen.

31. Use of a lentivirus engineered to comprise nucleic acid encoding said antigen, or an antigen presenting cell (e.g. a dendritic cell) transduced in vitro with a lentiviral vector engineered to comprise nucleic acid encoding said antigen such that said dendritic cell expresses said antigen, in the preparation of a pharmaceutical composition for the priming or boosting of an immune response against the antigen in a heterologous prime-boost immunisation protocol, wherein the composition is for use in conjunction with a second pharmaceutical composition encoding or containing said antigen, the second pharmaceutical composition being used for the boosting or priming respectively of said immune response.

32. Use according to claim 31 wherein the pharmaceutical composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and wherein the composition is for use in priming an immune response in conjunction with a boosting composition comprising a pox virus having a modified genome encoding said antigen.

33. Use according to claim 31 wherein the pharmaceutical composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and wherein the

composition is for use in priming an immune response against said antigen in conjunction with a boosting composition comprising an immunologically different lentiviral vector engineered to comprise nucleic acid encoding said antigen.

34. Use according to claim 30 wherein the pharmaceutical composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and is for use in boosting an immune response against said antigen in conjunction with a priming composition comprising an immunologically different lentiviral vector engineered to comprise nucleic acid encoding said antigen.

35. Use according to claim 30 wherein the pharmaceutical composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and is for use in boosting an immune response against said antigen in conjunction with a priming composition comprising a nucleic acid encoding said antigen.

36. Use according to claim 30 wherein the pharmaceutical composition comprises a lentiviral vector engineered to comprise nucleic acid encoding said antigen, and is for use in boosting an immune response against said antigen, in conjunction with a priming composition comprising a pox virus having a modified genome encoding said antigen.

37. Use according to claim 30 wherein the pharmaceutical composition comprises antigen presenting cells transduced in vitro with a lentiviral vector engineered to comprise nucleic acid encoding said antigen such that the cells express said antigen, and is for use in priming an immune response against said antigen in conjunction with a boosting composition comprising a pox virus, preferably a vaccinia virus, having a modified genome encoding said antigen.